Morning Blood Pressure Surge is Associated with Arterial Stiffness and Sympathetic Baroreflex Sensitivity in Hypertensive Seniors

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Abstract

Morning blood pressure (BP) surge is considered to be an independent risk factor for cardiovascular diseases. We tested the hypothesis that increased large-artery stiffness and impaired sympathetic baroreflex sensitivity (BRS) contribute to augmented morning surge in elderly hypertensives. Morning surge was assessed as morning systolic BP averaged for 2 hours just after waking up minus minimal sleeping systolic BP by using ambulatory BP monitoring (ABPM) in 40 untreated hypertensives [68±1 (SE) yrs] and 30 normotensives (68±1 yrs). Beat-by-beat finger BP and muscle sympathetic nerve activity (MSNA) were recorded in the supine position and at 60° upright tilt. We assessed arterial stiffness with carotid-to-femoral pulse wave velocity (cfPWV) and sympathetic BRS during spontaneous breathing. Awake and asleep ABPM-BPs and morning surge were higher in hypertensives than normotensives (all P<0.001). cfPWV was higher (P=0.002) and sympathetic BRS was lower (P=0.096) in hypertensives than normotensives. Hypertensives with morning surge ≥35 mmHg (median value) had higher cfPWV (11.9±0.5 vs 9.9±0.4 m·s⁻¹, P=0.002) and lower sympathetic BRS (supine: –2.71±0.25 vs –3.73±0.29, P=0.011; upright: –2.62±0.22 vs –3.51±0.35 bursts·100 beats⁻¹·mmHg⁻¹, P=0.052) than those with morning surge <35 mmHg. MSNA indices were similar between groups (all P>0.05), while upright total peripheral resistance was higher in hypertensives with greater morning surge than those with lesser morning surge (P=0.050). Morning surge was correlated positively with cfPWV (r=0.59, P<0.001) and negatively with sympathetic BRS (r=0.51, P<0.001) in hypertensives only. Thus, morning BP surge is associated with arterial stiffness and sympathetic baroreflex sensitivity, as well as vasoreactivity during orthostasis in hypertensive seniors.

Key words: Circadian rhythm, sympathetic nerve activity, hypertension, aging
Introduction

In humans, blood pressure (BP) shows circadian variations; it decreases during sleep and increases in the morning (19,36). Cardiovascular events also have a distinct circadian pattern with a peak incidence in the morning (5,19). The degree of morning BP surge from the nadir during the night has been found to be an independent predictor for cardiovascular events (12,15) and therefore, elderly hypertensive patients who have poor morning BP control (26) may be at higher risk of these events. Thus, it is important to evaluate the pathophysiological mechanisms underlying the morning surge in elderly hypertensives.

Some studies have demonstrated that the morning surge is associated with arterial stiffness and autonomic function. For example, hypertensive patients with an exaggerated morning surge ≥ 50 mmHg in systolic BP (SBP) or ≥ 22 mmHg in diastolic BP (DBP) had higher levels of carotid intima-media thickness and urinary catecholamine excretion than those with lesser morning surge (17). Cardiovagal baroreflex sensitivity (BRS), which regulates BP at the heart through the autonomic nervous system, was negatively correlated with morning SBP (4). Moreover, it was found that a decreased cardiovagal BRS was caused by a reduction in distensibility of the carotid artery, especially during the BP rise in the morning (33). Therefore, it seems that hypertensive patients with greater arterial stiffness have a lesser ability to buffer against BP increases in the morning. Based on the finding that the contribution of total peripheral resistance (TPR) to BP change by orthostasis became greater, while the contribution of heart rate (HR) decreased with age in hypertensives (16), the sympathetic baroreflex, which regulates BP via vasoconstriction, may play a more important role in control of morning BP in elderly hypertensives. The morning surge is actually assessed with night time BP and morning BP for 2 h after waking up (12), suggesting that the morning surge includes BP rises upon standing.
Therefore, sympathetic control of BP during upright posture may also affect the magnitude of the morning surge. However, there is no information available regarding the effect of supine or upright sympathetic BRS on the morning surge in humans.

We recently reported that sympathetic BRS was correlated with the stiffness of the barosensory artery—the carotid artery and aorta in elderly individuals (21). Because it seems that elderly hypertensives with higher arterial stiffness have lower sympathetic BRS, we hypothesized that impaired sympathetic BRS and higher arterial stiffness would be observed in elderly hypertensives with greater morning surge, and that the level of morning surge would be correlated with sympathetic BRS. Additionally, elderly hypertensives with enhanced $\alpha_1$-adrenergic responsiveness were found to have a greater increase in BP by norepinephrine infusion even with a similar increase of sympathetic nerve activity compared to elderly normotensives (32). Therefore, we also evaluated muscle sympathetic nerve activity (MSNA) during head-up tilt to test whether the efficacy of change in MSNA on TPR by head-up tilt is higher and/or upright sympathetic BRS is lower in elderly hypertensives with greater morning surge than those with lesser morning surge or normotensives.

**Methods**

**Subjects**

Two hundred and ninety-four elderly individuals in the Dallas-Fort Worth area were contacted between August 2008 and May 2011, and 138 of them were interested in participating in research and were screened for our study. Ultimately, 70 elderly volunteers [40 hypertensives (awake SBP: 135-159 and/or awake DBP: 85-99 mmHg according to 24-h ambulatory BP monitoring, ABPM) (2) and 30 normotensives] participated in and completed the study. All
participants were screened with a careful medical history, physical examination, 12-lead electrocardiogram, fasting blood samples, 24-h urine collection, and cardiovascular- and abdominal-echogram to confirm that they had no overt history of chronic diseases (e.g., cardiopulmonary, neurological, renal diseases, renal artery stenosis, primary aldosteronism, diabetes mellitus, and sleep apnea) which can cause secondary hypertension. They were excluded if they were smokers, regularly exercised at moderate-to-high intensity levels for >30 min/day for >3 times/week, or their body mass index was >35 kg·m\(^{-2}\). Women taking hormone replacement treatment were also excluded. Subjects gave their written informed consent to a protocol approved by the Institutional Review Boards of UT Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas. Subjects’ characteristics are presented in Table 1.

Measurements

**Muscle sympathetic nerve activity.** MSNA signals were obtained with microneurography (30,31). Briefly, a recording electrode was placed in the peroneal nerve at the popliteal fossa, and a reference electrode was placed subcutaneously 2-3 cm apart from the recording electrode. The nerve signals were amplified (70 000 to 160 000-fold), band-pass filtered (700 to 2000 Hz), full-wave rectified, and integrated with a resistance-capacitance circuit (time constant 0.1 sec). Criteria for adequate MSNA recordings include: pulse synchrony; facilitation during the hypotension phase of the Valsalva maneuver, and suppression during the hypertensive overshoot phase after release; and insensitivity to emotional stimuli (37).

**Hemodynamics.** HR was determined from the electrocardiogram (lead II) and beat-by-beat BP was derived by finger photoplethysmography (Nexfin, BMEYE, Amsterdam, The Netherlands).
Arm cuff BP was measured by electrosphygmomanometry (model 4240, SunTech Medical Instruments Inc., Raleigh, NC) with a microphone placed over the brachial artery to detect Korotkoff sounds. Carotid and femoral arterial pressure waveforms were obtained with a pencil-sized tonometer (SphygmoCor, AtCor Medical, Sydney, Australia). Cardiac output was measured via the modified acetylene rebreathing technique (10). Stroke volume was calculated from cardiac output divided by HR, and TPR was calculated as the quotient of mean BP and cardiac output, multiplied by 80, where variables were measured during rebreathing. Respiratory excursions were detected by a nasal cannula.

24-h ambulatory blood pressure monitoring. The ABPM device (Oscar 2, SunTech Medical Instruments Inc.) automatically measured BP and HR using the oscilometric method every 30 min during the awake period and every 30-60 min during the sleep period throughout the 24-h cycle (12,15).

Protocol

Patients who had been taking antihypertensive medications were progressively weaned from these drugs for ~2 weeks. All subjects underwent a 3-week run-in period before testing, and they were instructed to maintain a healthy lifestyle according to the Seventh Report of the Joint National Committee standard guidelines (2). 24-h ABPM was repeated after this period. We used 24-h ABPM with the subjects’ report and diary documenting the waking and sleeping time to evaluate morning surge. If they had poor sleep quality, they repeated 24-h ABPM. Prior to testing, all subjects consumed a 3 day isocaloric constant diet consisting of: 100 mEq sodium,
100 mEq potassium, and 1000 mg calcium daily to minimize the effects of salt intake on MSNA. Fluid intake was *ad libitum.*

The experiment was performed in a quiet, environmentally controlled laboratory with an ambient temperature of ~25°C. Subjects came to the laboratory early in the morning, ≥72 h after the last caffeinated or alcoholic beverage and ≥24 h after strenuous physical activity, and were placed in the supine position. At least 10 min after a satisfactory nerve recording site had been found, MSNA signals were recorded for 6 min during spontaneous breathing. All participants then performed two Valsalva maneuvers at 40 mmHg for 20 s with approximately 5 min apart. Thereafter, 60° upright tilt was conducted for 10 min and MSNA data were collected during the last 3 min of tilting. Since the day-to-day variability of MSNA is small and the reproducibility of the measurement is high (31), arterial stiffness was assessed the next morning to avoid the effect of fatigue on the autonomic nervous system and then arterial stiffness because of the lengthy study. After >30 min of supine rest, baseline hemodynamics were measured. Carotid and femoral arterial pressure waveforms were obtained simultaneously with the electrocardiogram.

**Data analysis**

Data were sampled at 625 Hz and stored on personal computer with a commercial data acquisition system (AcqKnowledge, Biopac System, Santa Barbara, CA). Off-line data analyses were performed using signal-processing software (LabView, National Instruments, Austin, TX). Sympathetic bursts were identified by a computer program (21), and then confirmed by an experienced microneurographer. The integrated neurogram was normalized by assigning a value of 100 to the largest amplitude of a sympathetic burst during the 6-min data collection (13). Burst area was measured as the area under the curve of each sympathetic burst on a beat-by-beat
basis. The number of bursts per minute (burst frequency), the number of bursts per 100 heart beats (burst incidence), and total burst area per minute (total activity) were used as quantitative indices. The efficacy of MSNA for vasoconstriction was assessed with a %change in TPR divided by %change in MSNA burst frequency by upright tilt.

**Morning surge.** We defined morning surge as the morning SBP (averaged SBP for 2 h just after wake-up) minus the lowest nocturnal SBP by using ABPM after the run-in period (sleep-through morning surge)(12). We found similar results by using sleep-through morning surge and preawakening morning surge calculated with averaged SBP for 2 h before waking up instead of the lowest nocturnal SBP. Morning HR increase was defined using the same formula.

**Arterial stiffness.** We used carotid-to-femoral pulse wave velocity (cfPWV) as an index of large-artery stiffness (14). A foot-to-foot methodology was employed to determine pressure wave transit time at the carotid and femoral artery in relation to the R-wave of electrocardiogram. Pulse transit length was estimated by subtracting the distance between sternal notch and the measuring point at the carotid artery from the distance between sternal notch and the measuring point at the femoral artery. cfPWV was calculated from the transit length divided by the transit time.

**Baroreflex sensitivity.** Sympathetic BRS was assessed by using the slope of the linear correlation between MSNA and DBP during spontaneous breathing in each subject (6,30) after confirming that r value was >0.5 as described previously (27). MSNA burst incidence was calculated over a 3-mmHg DBP bin (6,21), and statistically weighted to reduce the impacts of
inherent non-baroreflex variability (e.g. respiration) and minor variation of bin width and position (13). Cardiovagal BRS was assessed by averaging the values of the slope of the linear correlation between R-R interval and beat-by-beat SBP during the two Valsalva maneuvers in each subject after confirming r value was >0.8 (18). Values for SBP were linearly regressed against corresponding R-R interval (lag 1)(18) during the hypertensive phase (phase IV), which was in the same direction of BP change with morning surge.

Statistical analysis

Values are expressed as means±SE. Linear regression analysis was used to evaluate the correlation between morning surge and arterial stiffness, sympathetic, and cardiovagal BRS. Data between hypertensives and normotensives were compared using unpaired t-tests. If normality tests and/or equal variance tests failed, we compared the differences between groups using Mann-Whitney Rank Sum Tests. Multiple regression analysis was used to assess factors related with morning surge in elderly hypertensives and normotensives, respectively. A P value of <0.05 was considered statistically significant.

Results

Ambulatory blood pressure and heart rate

ABPM-BPs were higher in hypertensives than normotensives for all periods; 24 h, awake, and asleep (Table 2). Both the lowest nocturnal SBP and morning SBP were higher in hypertensives than normotensives with no difference in night time dip in SBP. ABPM-HR was not different between groups in any period.
Supine resting variables

Table 3 depicts hemodynamics and MSNA indices during supine rest. Supine BP was similar to asleep ABPM-BP in both hypertensives and normotensives, while all supine BPs were still higher in hypertensives than normotensives. There were no differences in HR, stroke volume, and cardiac output between groups, while TPR was higher in hypertensives than normotensives (P=0.081). All MSNA indices were similar between groups.

Morning surge, arterial stiffness, and baroreflex sensitivity

Morning surge was greater in hypertensives than normotensives, but morning HR increase was similar between groups (Figure 1A & B). cfPWV was higher in hypertensives than normotensives (Figure 1C). Sympathetic BRS was lower in hypertensives than normotensives (P=0.096), but cardiovagal BRS was similar between groups (Figure 1D & E). To compare these variables between hypertensives with greater and lesser morning surge, we set the median of morning surge (35 mmHg) as a threshold and divided hypertensives into 2 subgroups (Figure 2A); those with morning surge ≥35 mmHg (n=20) and <35 mmHg (n=20) [similar age and physical characteristics (all P>0.050) and the same men-to-women ratio (10:10) between subgroups]. Likewise, between subgroups, morning HR increase and cardiovagal BRS were similar (Figure 2B & E), while cfPWV was higher and sympathetic BRS was lower in hypertensives with morning surge ≥35 mmHg than those with morning surge <35 mmHg (Figure 2C & D).

In hypertensives, morning surge was positively correlated with cfPWV (Figure 3A), and negatively correlated with sympathetic BRS (Figure 3B). However, morning surge was not correlated with cardiovagal BRS (Figure 3C), MSNA burst frequency (r=0.10, P=0.529) or total
activity \((r=0.08, P=0.609)\). In normotensives, morning surge was not correlated with cfPWV 231 (Figure 3D), sympathetic BRS (Figure 3E), cardiovagal BRS (Figure 3F) or MSNA indices 232 (burst frequency: \(r=-0.29, P=0.124\) burst incidence: \(r=0.08, P=0.689\), or total activity: \(r=-0.14, P=0.689\)). Multiple regression analysis showed that cfPWV and sympathetic BRS were relatively 235 strong factors for morning surge in hypertensives, while cardiovagal BRS and morning HR 236 increase tended to be correlated with morning surge in normotensives (Table 4).

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**Upright sympathetic baroreflex sensitivity and vasoreactivity**

There was no difference in upright sympathetic BRS, %TPR/%MSNA, upright MSNA 239 burst frequency or TPR between elderly hypertensives and normotensives (Figure 4). Upright 240 sympathetic BRS was smaller \((P=0.052, \text{Figure 5A})\) and %TPR/%MSNA by 60° head-up tilt 241 was higher \((P=0.090, \text{Figure 5B})\) in hypertensives with morning surge \(\geq 35\) mmHg than those 242 with morning surge <35 mmHg. Although there was no difference in upright MSNA burst 243 frequency between hypertensive subgroups (Figure 5C), upright TPR was higher in 244 hypertensives with greater morning surge than those with lesser morning surge (Figure 5D). 245 Sympathetic BRS, but not %TPR/%MSNA, was correlated with cfPWV in hypertensives 246 (Figure 6).

247

**Discussion**

The major findings from this study are that (1) cfPWV was higher and sympathetic BRS 250 was lower in elderly hypertensives, especially those with greater morning surge than in elderly 251 normotensives; (2) morning surge was correlated with cfPWV and sympathetic BRS in 252 hypertensives only; and (3) there was no difference in supine or upright MSNA indices between
the groups, while the change in TPR for a given change in MSNA during head-up tilt was greater in hypertensives with greater morning surge than those with lesser morning surge. These results suggest that morning surge is associated with sympathetic baroreflex sensitivity and vasoreactivity to orthostasis, as well as arterial stiffness, in elderly hypertensives.

**Sympathetic neural control of blood pressure in the morning**

Morning surge has been proposed to be related to an excessive increase of sympathetic activity in the morning. This notion is supported by the Hypertension and Lipid Trial (HALT) (22) indicating that α-adrenergic blockade decreased morning BP. Kario et al. (11) demonstrated that original (baseline) morning surge had a strong correlation with a reduction of the morning surge by α-adrenergic blockade, doxazosin. Conversely, we and others (8) found no correlation between morning surge and MSNA in hypertensive patients. This discrepancy suggests that other sympathetic neural control system(s), rather than absolute MSNA, may be responsible for the morning surge. If sympathetic baroreflex function were maintained in hypertensives with greater morning surge, MSNA should have been reduced when BP increased markedly in the morning, and morning absolute MSNA should have been negatively correlated with morning surge. The absence of a relationship between morning surge and MSNA in hypertensives suggests that sympathetic BRS in the patients with higher morning surge may be impaired and/or the baroreflex curve may be reset to a higher BP level in the morning. Indeed, hypertensives with morning surge ≥35 mmHg, which was similar to the median value for elderly hypertensives in a previous study (39), had a lower sympathetic BRS than hypertensives with morning surge <35 mmHg, while the latter had similar sympathetic BRS to that of normotensives. Sympathetic BRS was found to decrease while sleeping and increase while awake (20). Moreover, it was found that
the MSNA response was enhanced and the HR response was unchanged or lessened to the change in BP during orthostasis (16), mental stress (1), cold stress (9), and exercise (34) with age especially in hypertensives (3,16). Therefore, in elderly hypertensives, baroreflex control of TPR through MSNA seems to be predominant compared to baroreflex control of HR in the BP regulation at the time of awaking. The negative correlation between morning surge and sympathetic BRS and an exaggerated increase in TPR in the morning (36) in hypertensives suggest that impaired sympathetic baroreflex function may result in the lack of a buffer system against morning surge in elderly hypertensives.

There are some studies focusing on the circadian pattern of cardiovagal BRS. All of them demonstrated that a reduction of cardiovagal BRS occurred concomitant with BP increase in the morning, and it was suggested that cardiovagal BRS may be one of the determining factors for morning surge (4,33,36). Given the fact that a reduction of cardiovagal BRS and its correlation with morning BP were also observed in healthy normotensives (4,33) and that this relationship disappeared in hypertensive seniors in the current study, cardiovagal BRS may not be a predominant factor for morning BP increase in elderly hypertensives. Indeed, multiple regression analysis showed that the lower cardiovagal BRS tended to be the factor for the higher morning surge in normotensives, but not in elderly hypertensives whose morning surge was significantly impacted by sympathetic BRS.

Orthostatic effects

Morning surge includes the pressor response to orthostasis after awakening. The current study showed that upright sympathetic BRS was also lower in hypertensives with morning surge ≥35 than those with morning surge <35 mmHg, suggesting that impaired upright sympathetic
baroreflex function may be, at least partially, related to the morning surge evoked by orthostasis. However, the difference of upright sympathetic BRS between hypertensive subgroups categorized by morning surge was weaker than the difference of supine sympathetic BRS between them (P=0.052 vs 0.011). This suggests that morning surge during orthostasis may be also affected by other mechanisms. One of the other possible sympathetic systems influencing morning surge may be vasoreactivity to a change in MSNA. In this study, the efficacy of the increase in MSNA by head-up tilt on TPR was greater in hypertensives with greater morning surge than those with lesser morning surge. Therefore, upright TPR was significantly higher in hypertensives with greater morning surge despite upright MSNA being similar to those with lesser morning surge. This greater efficacy of MSNA on TPR during head-up tilt may be attributable to a greater sympathetic vascular transduction via augmented $\alpha_1$-adrenergic responsiveness observed in elderly hypertensives in the previous study (32) and/or the enhanced renin-angiotensin-aldosterone system.

Arterial stiffness and morning surge

To our knowledge, there are only two studies published evaluating the relationship between morning surge and cfPWV. Both studies demonstrated that morning surge was significantly correlated with cfPWV in subjects including patients with type 2 diabetes, and untreated and treated hypertension (23,28). We found in elderly hypertensives that morning surge was correlated with both sympathetic BRS and cfPWV and that there was a significant correlation between sympathetic BRS and cfPWV. There seems to be a close link between morning surge, arterial stiffening, and impaired sympathetic baroreflex function. Since baroreceptors are stretch receptors, the distortion of the barosensory artery is required to initiate
neural firing. Taylor et al. (33) found that the decrease in cardiovagal BRS in the morning was due to a reduced carotid artery distortion by the change in BP but not a blunted neural response to the distortion. Because the mechanical change of the artery is a common component between the cardiovagal and sympathetic baroreflex, higher arterial stiffness could suppress the day time increase in sympathetic BRS. Conversely, no relationship between the efficacy of change in MSNA on TPR and cfPWV during upright posture was observed in this study, suggesting that vasoreactivity may be independent of arterial stiffness as a factor for the morning surge. Since this study was designed as a descriptive study, we cannot demonstrate cause-effect relationships; however, it is possible that stiffening of the arteries may cause enhanced morning surge via the lower sympathetic BRS.

Perspectives

The synergistic effects of a smaller decrease of MSNA even with a greater BP increase due to impaired supine and upright sympathetic BRS and greater vasoreactivity to MSNA by standing up may result in enhanced morning surge in elderly hypertensives. This could place hypertensive patients at a higher risk for cardiovascular events. This study may provide some insight into the best treatment strategy for elderly hypertensives with greater morning surge. Recently, the large-scale, international, multicenter SURGE study clearly demonstrated that morning BP was higher than lunch time and evening BP in elderly hypertensives whose morning BP control was very poor (control rate 13.1%) even with anti-hypertensive drugs (26). Pharmacological and non-pharmacological approaches that can decrease large-artery stiffness, increase sympathetic BRS, and attenuate sympathetic vasoconstriction for 24 hours may be particularly effective in reducing cardiovascular risks in these patients. Conversely, Verdecchia...
et al. (38) reported controversial relationships between morning surge and cardiovascular events; blunted morning surge was a predictor of cardiovascular events, while increased morning surge did not change the risk. This discrepancy seemed to be due to the interaction of morning BP rise and nocturnal BP dip; a smaller nocturnal dip in BP, another risk factor for cardiovascular events, resulted in a smaller morning surge. It seems to be necessary to distinguish morning surge caused by morning BP rise and that by nocturnal BP dip.

**Limitations**

First, consistent with the results of a previous study (39), the repeatability coefficient expressed as percentage of maximal variation was 39.7% for hypertensives and 62.9% for normotensives. The relatively low reproducibility of the morning surge especially in normotensives may obscure significant relationships between morning surge, cfPWV, and sympathetic BRS. However, even BP conventionally used in clinics exhibited a similar repeatability (~50%) to the morning surge (35) and many reports have indicated the significance of morning surge as a predictor for cardiovascular events in hypertensives (12,15). Therefore, we believe that our results are reliable and may provide insight into the underlying mechanisms of the increased morning surge for cardiovascular diseases in elderly hypertensives. Second, we used cfPWV to assess arterial stiffness. It was found that cfPWV was affected by BP (29). However, cfPWV normalized by mean BP showed a similar relationship with morning surge (hypertensives: r=0.53, P<0.001; normotensives: r=-0.38, P=0.040) as that with original cfPWV. Third, sympathetic BRS was evaluated during spontaneous breathing. Thus, the sensitivity was measured without assessing the entire baroreflex curve, which includes non-baroreflex BP fluctuations. However, we used the binning method with MSNA burst incidence to reduce the
impact of non-baroreflex influence (30). Therefore, we can reveal the physiological modulation of sympathetic control around prevailing and operating point (6). Fourth, although we excluded patients with diagnosed sleep apnea, patients with unknown sleep apnea might have been included, because we did not perform polysomnography. However, it has been reported that patients with and without sleep apnea do not have any difference of the morning surge (24).

Fifth, although we evaluated supine sympathetic BRS and cfPWV as factors of morning surge, they were measured at different time points from the period when a part of morning surge occurs--before waking up. Conversely, upright sympathetic BRS and %TPR/%MSNA were measured in a similar situation to when a part of morning surge occurs--orthostasis after waking up. Sixth, our subjects on average were considered overweight because of the difficulty to find elderly individuals who were healthy (except for stage I hypertension in the patient group), sedentary, but not overweight in the Dallas-Fort Worth area. However, there was no difference in weight or body mass index between groups in our study. Finally, we excluded patients with stage-II hypertension for safety reasons. Although we found no difference in MSNA between hypertensives and normotensives, which was similar to previous findings in borderline hypertensive patients (25), MSNA in moderate-to-severe middle-aged hypertensives was found to be higher than that in normotensives (7). Whether similar results can be obtained in elderly patients with stage-II and white-coat hypertension needs to be determined.

In summary, elderly hypertensives with greater morning surge had higher arterial stiffness and smaller sympathetic baroreflex sensitivity than those with lesser morning surge. In addition, morning blood pressure surge was positively correlated with arterial stiffness, while both variables were negatively correlated with sympathetic baroreflex sensitivity in elderly...
hypertensives. Furthermore, smaller sympathetic baroreflex sensitivity and greater total peripheral resistance with similar MSNA were observed in hypertensives with greater morning surge during upright posture. These results suggest that morning surge may be associated with sympathetic baroreflex sensitivity altering concomitantly with large-artery stiffness and vasoconstrictor sensitivity (e.g., sympathetic vascular transduction) during orthostasis in elderly hypertensives.
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Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).
References


Figure Legends

Figure 1: Morning blood pressure surge (A), heart rate (HR) increase in the morning (B), carotid-to-femoral pulse wave velocity (cfPWV, C), sympathetic baroreflex sensitivity (BRS, D), and cardiovagal BRS (E) in elderly hypertensives and normotensives. Values are means±SE.

Figure 2: Morning blood pressure surge (A), heart rate (HR) increase in the morning (B), carotid-to-femoral pulse wave velocity (cfPWV, C), sympathetic baroreflex sensitivity (BRS, D), and cardiovagal BRS (E) in elderly hypertensives with morning surge ≥35 mmHg and those with morning surge <35 mmHg. Values are means±SE.

Figure 3: Linear regression analysis of the inter-individual relationships between morning blood pressure surge and carotid-to-femoral pulse wave velocity (cfPWV, A and D), sympathetic baroreflex sensitivity (BRS, B and E), and cardiovagal BRS (C and F) in elderly hypertensives and normotensives.

Figure 4: Upright sympathetic baroreflex sensitivity (BRS, A), efficacy of muscle sympathetic nerve activity (MSNA) on total peripheral resistance (TPR) from supine to upright (B), upright MSAN burst frequency (C), and upright TPR (D) in elderly hypertensives and normotensives. Values are mean±SE.

Figure 5: Upright sympathetic baroreflex sensitivity (BRS, A), efficacy of muscle sympathetic nerve activity (MSNA) on total peripheral resistance (TPR) from supine to upright (B), upright
MSAN burst frequency (C), and upright TPR (D) in elderly hypertensives with morning surge $\geq 35$ mmHg and those with morning surge $<35$ mmHg. Values are mean±SE.

**Figure 6:** Linear regression analysis of the inter-individual relationships between sympathetic baroreflex sensitivity (BRS) and carotid-to-femoral pulse wave velocity (cfPWV, $A$) and between efficacy of muscle sympathetic nerve activity (MSNA) on total peripheral resistance (TPR) and cfPWV ($B$) in elderly hypertensives.
Figure 1. Okada et al.
Hypertensives, morning surge ≥35 mmHg

Hypertensives, morning surge <35 mmHg

Figure 2. Okada et al.
Hypertensives

- morning surge ≥35 mmHg
- morning surge <35 mmHg

\[ y = 3.32x + 0.48 \]
\[ r = 0.59 \]
\[ P < 0.001 \]

Normotensives

\[ r = -0.35 \]
\[ P = 0.055 \]

B

\[ y = 4.86x + 51.42 \]
\[ r = 0.51 \]
\[ P < 0.001 \]

E

\[ r = -0.12 \]
\[ P = 0.522 \]

C

\[ r = -0.15 \]
\[ P = 0.363 \]

F

\[ r = 0.07 \]
\[ P = 0.722 \]

Figure 3. Okada et al.
Figure 4. Okada et al.
Hypertensives, morning surge ≥ 35 mmHg

Hypertensives, morning surge < 35 mmHg

Figure 5. Okada et al.
Hypertensives with morning surge $\geq 35$ mmHg

Hypertensives with morning surge $< 35$ mmHg

\[ Y = 0.23x - 5.71 \]
\[ r = 0.38 \]
\[ P = 0.015 \]

\[ r = 0.22 \]
\[ P = 0.114 \]

Figure 6. Okada et al.
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Values are means ± S.E.
Table 2. 24-h ambulatory blood pressure and heart rate

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypertensives</th>
<th>Normotensives</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPM-SBP, mmHg</td>
<td>24h</td>
<td>142±1</td>
<td>121±1</td>
</tr>
<tr>
<td></td>
<td>Awake</td>
<td>147±2</td>
<td>124±1</td>
</tr>
<tr>
<td></td>
<td>Asleep</td>
<td>129±2</td>
<td>110±1</td>
</tr>
<tr>
<td>ABPM-DBP, mmHg</td>
<td>24h</td>
<td>79±1</td>
<td>70±1</td>
</tr>
<tr>
<td></td>
<td>Awake</td>
<td>81±1</td>
<td>73±1</td>
</tr>
<tr>
<td></td>
<td>Asleep</td>
<td>70±1</td>
<td>61±1</td>
</tr>
<tr>
<td>Morning SBP, mmHg</td>
<td></td>
<td>147±2</td>
<td>121±1</td>
</tr>
<tr>
<td>The lowest nocturnal SBP, mmHg</td>
<td>111±2</td>
<td>97±1</td>
<td></td>
</tr>
<tr>
<td>Night time dip in SBP, %</td>
<td>12±2</td>
<td>11±1</td>
<td></td>
</tr>
<tr>
<td>ABPM-HR, beats·min⁻¹</td>
<td>24h</td>
<td>69±1</td>
<td>71±2</td>
</tr>
<tr>
<td></td>
<td>Awake</td>
<td>72±1</td>
<td>74±2</td>
</tr>
<tr>
<td></td>
<td>Asleep</td>
<td>63±1</td>
<td>63±1</td>
</tr>
<tr>
<td>Morning HR, beats·min⁻¹</td>
<td>69±2</td>
<td>71±2</td>
<td></td>
</tr>
<tr>
<td>The lowest nocturnal HR, beats·min⁻¹</td>
<td>56±1</td>
<td>56±1</td>
<td></td>
</tr>
</tbody>
</table>

ABPM indicates ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Values are means ± S.E.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypertensives</th>
<th>Normotensives</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>128±2</td>
<td>112±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>72±2</td>
<td>66±2</td>
<td>0.006</td>
</tr>
<tr>
<td>HR, beats·min⁻¹</td>
<td>66±1</td>
<td>68±2</td>
<td>0.374</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>61±2</td>
<td>61±3</td>
<td>0.744</td>
</tr>
<tr>
<td>Cardiac output, l·min⁻¹</td>
<td>4.0±0.1</td>
<td>4.1±0.2</td>
<td>0.653</td>
</tr>
<tr>
<td>TPR, dyne·s·cm⁻⁵</td>
<td>1708±46</td>
<td>1570±66</td>
<td>0.081</td>
</tr>
<tr>
<td>MSNA burst frequency, bursts·min⁻¹</td>
<td>40±1</td>
<td>40±2</td>
<td>0.986</td>
</tr>
<tr>
<td>MSNA burst incidence, bursts·100beats⁻¹</td>
<td>65±2</td>
<td>65±2</td>
<td>0.974</td>
</tr>
<tr>
<td>Total activity, unit·min⁻¹</td>
<td>573±24</td>
<td>591±35</td>
<td>0.650</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TPR, total peripheral resistance; MSNA, muscle sympathetic nerve activity. Values are means ± S.E.
<table>
<thead>
<tr>
<th></th>
<th>Hypertensives</th>
<th>Normotensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple $r^2$</td>
<td>0.58</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
</tr>
<tr>
<td>cfPWV, mmHg</td>
<td>0.458</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The lowest nocturnal SBP, mmHg</td>
<td>Excluded variable</td>
<td>-0.275</td>
</tr>
<tr>
<td>Morning SBP, mmHg</td>
<td>-0.047</td>
<td>0.834</td>
</tr>
<tr>
<td>Dip of night HR, beats·min$^{-1}$</td>
<td>-0.290</td>
<td>0.040</td>
</tr>
<tr>
<td>Morning HR increase, beats·min$^{-1}$</td>
<td>0.093</td>
<td>0.660</td>
</tr>
<tr>
<td>Total activity, unit·min$^{-1}$</td>
<td>0.036</td>
<td>0.799</td>
</tr>
<tr>
<td>Sympathetic BRS, bursts·100 beats$^{-1}$·mmHg$^{-1}$</td>
<td>0.332</td>
<td>0.023</td>
</tr>
<tr>
<td>Cardiovagal BRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase IV, ms·mmHg$^{-1}$</td>
<td>0.057</td>
<td>0.668</td>
</tr>
</tbody>
</table>

PWV indicates pulse wave velocity; SBP, systolic blood pressure; HR, heart rate; BRS, baroreflex sensitivity.